REMARKS

Introductory Comments:

Claims 1, 4-19 and 32 were examined in the Office Action under reply and rejected soley under 35 U.S.C. §103(a). This rejection is believed to be overcome for reasons discussed below.

Overview of the Above Amendments:

Claims 1, 5, 6, 9 and 32 have been amended herein to recite the subject invention with greater particularity. Specifically, claim 1 now recites that the polypeptide is immunogenic and defines the deletion present in the NS3 polypeptide with reference to the HCV-1 sequence. Antecedent basis for the amended dependent claims has also been provided. New claims 43-50 have been added. Claim 43 further defines the mutant NS3 sequence as having the deletion specified in claim 1 but comprising the remainder of the NS3 sequence. New claims 44 and 45 depend from claim 43 and correspond to claims 4 and 5, respectively. New claim 46 recites that the polypeptide "consists of" the sequence of amino acids of SEQ ID NO:9. New claims 47-50 correspond to claim 19 but depend from claims 12, 32, 43 and 46, respectively.

Support for the foregoing amendments and new claims can be found in the original claims, as well as throughout the specification at, e.g., page 11, lines 17-20; page 49, line 15; and in the examples.

The foregoing amendments are made without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record.

The Cited Art:

Claims 1, 4-19 and 32 were rejected under 35 U.S.C. §103(a) as unpatentable over Bartenschlager et al., *J. Virol.* (1993) 67:3835-3844 ("Bartenschlager") in view of EP Publ. No. 693,687 to Houghton et al. ("Houghton") and U.S. Patent No. 5,372,928 to Miyamura et al. ("Miyamura"). The Office recognizes that Bartenschlager fails to teach a deletion of at least 200 amino acids from the N-terminus of the NS3 domain. The Office also acknowledges the reasons for the lack of protease activity are unclear. However, the Office argues "Bartenschlager demonstrate (Figure 5) that a deletion of 60 amino acids rendered the protease non-functional...The polypeptide of Bartenschlager and the claimed polypeptide are functional equivalents, since both polypeptides contain the deletion that disrupts catalytic activity." Office Action, page 3. However, applicants disagree with the Office's reasoning.

In particular, just because one molecule functions similarly to a second molecule does not necessarily render the second molecule obvious. Rather, the question is whether the prior art suggests making the specific molecular modifications necessary to achieve the claimed invention. See, *In re Deuel*, 34 USPQ2d 1210, 1214; *In re Jones*, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990); *In re Grabiak*, 226 USPQ 870, 872 (Fed. Cir. 1985) ("[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/ [claimed] thioester change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant."); *In re Lalu*, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). Here, neither a reading of Bartenschlager alone, or in combination with Houghton and Miyamura, renders the claimed molecular modifications obvious.

Bartenschlager pertains to the characterization of the NS3 protease domain as it relates to HCV NS protein cleavage. Bartenschlager found that removal of the 60 N-terminal amino acids of the NS3 domain affected NS3/4 cleavage. However, Bartenschlager does not even remotely suggest deletion of the amino acid sequence corresponding to amino acids 1027-1241 of HCV-1, and does not address whether his 60 amino acid deletion mutant, let alone applicants' claimed deletion mutant, results in an immunogenic molecule. Even if Bartenschlager's molecule was inherently immunogenic, such is not a proper basis for an obviousness rejection. The Federal

Circuit has cautioned that the inherency of a characteristic of a compound does not make it obvious. As stated in *In re Newell*, 13 USPQ2d 1248 (Fed. Cir. 1989): "That which is inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Newell* at 1250, citing *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966). Bartenschlager fails entirely to teach or suggest NS3-containing polypeptides having the claimed characteristics. As acknowledged by the Examiner, Bartenschlager does not describe or demonstrate applicants' claimed deletions. Bartenschlager describes only N-terminal deletions of up to 60 amino acids and internal deletions including both N-terminal and C-terminal residues.

The Office further argues: "Even if the immunodominant region were deleted, other epitopes remain; otherwise the polypeptide would not be effective for inducing a therapeutic immune response. One of ordinary skill in the art would have been motivated to use the claimed deletion mutant in a composition because Houghton used an NS3 deletion mutant." Office Action, page 3. However, this statement is direct evidence of the hindsight reasoning being used by the Office. Applicants discovered that polypeptides including the deletion specified in the claims still retained immunogenicity. There was absolutely no expectation based on the cited art that HCV NS mutant polypeptides, having a deletion of the amino acid sequence corresponding to amino acids 1027-1241 of HCV-1, would function as claimed. Houghton is directed to combination HCV antigens comprising an antigen from the core domain of HCV and an additional HCV antigen. A preferred antigen from the NS3 domain specified in Houghton is C33c. C33c includes amino acids 1192-1457 of NS3. Thus, C33c lacks amino acids 1027-1191 and 1458-1657 of the NS3 domain. There is no suggestion in Houghton to make the particular deletions to the N-terminus of the NS3 claimed by applicants (namely, a deletion of the amino acid sequence corresponding to amino acids 1027-1241 of HCV-1) and to retain the C-terminal portion of the NS3 domain. Finally Miyamura is silent as to any deletions in NS3.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified, does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Without a suggestion to modify the references evident in the prior art as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Based on the foregoing, the rejection of the claims over the stated combination should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are patentable over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Please direct all further communications in this application to:

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Respectfully submitted,

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